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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,585	DONKENA ET AL.	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57,63-65 and 67-70* is/are pending in the application.

4a) Of the above claim(s) *3-65 and 67-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 January 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/18/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group 11 (claims 1-8, SEQ ID NO: 43, species A and E) in the reply filed on May 20, 2008 is acknowledged.

2. Claims 3, 4, 6-57, 63-65 and 67-70 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species and inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 20, 2008.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

4. Claims 1, 2 and 5 will be examined to the extent that they read on SEQ ID NO: 43, since the detection of mRNA was elected.

Priority

5. Since the provisional application No. 60/487,553 provides support for SEQ ID NO: 1-26, all of the other claimed sequences have the priority date of the PCT/US04/22850 application, namely, July 14, 2004.

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted on August 18, 2006 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Sequence Rules Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

APPLICANT IS GIVEN the time of response to this office action WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.F.R. §§ 1.821-1.825. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Figures 2a and 3b and their descriptions contain sequences without SEQ ID NOs to identify them. If these sequences are already included in the sequence listing submitted previously, Applicants should amend the drawings (or their descriptions) to identify the sequences by SEQ ID NOs. If these sequences were not previously submitted, a new sequence listing in paper and CRF format needs to be provide together with a letter stating that these two are the same.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 2 and 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the SOX4 for detecting the level of expression of at least 2.5-fold to distinguish between normal and G6 prostate cancer cells or normal and G9 prostate cancer cells in tissues obtained from prostate tumors, does not reasonably provide enablement for detecting or distinguishing between or among prostate cell proliferative disorders at any level of SOX4 expression in any other biological sample and for any sequence that hybridizes under high stringency conditions to SEQ ID NO: 43. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1, 2 and 5 are broadly drawn to a method for detecting, or for detecting and distinguishing between or among prostate cell proliferative disorders or stages thereof in a subject comprising: obtaining, from the subject, a biological sample; and determining, using a suitable assay, the expression level of at least one gene or sequence selected from the group consisting of: ZNF185 (SEQ ID NOS:1 and 2); PSP94 (SEQ ID NOS:29 and 30); BPAG1 (SEQ ID NO:31); SORBS1 (SEQ ID NOS:32 and 33); C21orf63 (SEQ ID NO:34); SVIL (SEQ ID NOS:35 and 36);

PRIMA1 (SEQ ID NO:37); FLJ14084 (SEQ ID NOS:38 and 39); TU3A (SEQ ID NOS:40 and 41); KIAA1210 (SEQ ID NO:42); SOX4 (SEQ ID NOS:43 and 44); MLP (SEQ ID NOS:45 and 46); FABP5 (SEQ ID NOS:47 and 48); MAL2 (SEQ ID NOS:49 and 50); Erg-2 (SEQ ID NOS: 51 and 52); and sequences that hybridize under high stringency thereto, whereby detecting and distinguishing between or among prostate cell proliferative disorders or stages thereof is, at least in part, afforded. However, as will be further discussed, there is no support in the specification and prior art for the method encompassing any level of expression or any level of increased expression of any of these sequences as detected in any biological sample. Further, there is no indication that any sequence which hybridizes to SEQ ID NO: 34 under stringent hybridization conditions when overexpressed will provide diagnostic information. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The issues discussed will be as follows:

i) detection or distinguishing between prostate cell proliferative disorders at any level of mRNA expression for SEQ ID NO: 34;

ii) detection or distinguishing between prostate cell proliferative disorders at any level of mRNA expression for sequences which hybridize under stringent conditions to SEQ ID NO: 34;

iii) detection or distinguishing between prostate cell proliferative disorders at any level of mRNA expression for SEQ ID NO: 34 in any biological sample.

Working Examples

The specification has working examples in which fifty genes were identified as having altered expression in prostate cancer cells, out of which four overexpressed genes (MLP, SOX4, FABP5 and Mal2) were confirmed as overexpressed by quantitative real-time RT-PCR. Analysis of the expression data for their significance with respect to association with stages and types of

prostate tumors for SOX4 provided statistically significant correlation between the overexpression of SOX4 at 2.5-fold or higher level with Grade 6 and Grade 9 tumors (Fig. 13, Table 3, page 76). The level of expression of SOX4 was not examined in any other biological sample (like blood or saliva, for example) in patients with prostate cancer. No sequences which hybridize under high stringency conditions to SEQ ID NO: 43 were examined for their level of expression in prostate tumor cells or any other biological samples.

Guidance in the Specification.

The specification provides no evidence that the disclosed level of overexpression of the SOX4 mRNA would be obtained in other biological samples such as blood or saliva. The specification also provides no indication that detecting increased levels of expression of polynucleotides hybridizing under stringent conditions to SEQ ID NO: 34 (unless they encoded SEQ ID NO: 44) in any sample would lead to detection of prostate cancer in a patient or to a discrimination between different cancer stages or types. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. As can be seen from the sequence search performed with the SOX4 sequence (accession No. X70683, which is 100% identical to SEQ ID NO: 43), there are at least 27 polynucleotides belonging to expressed genes which would hybridize under stringent conditions to SEQ ID NO: 43. Applicants did not show that detecting expression or increased expression of any of these polynucleotides in any biological samples would provide for diagnosis of prostate cancer or discrimination between prostate cancer types.

The unpredictability of the art and the state of art

There is a great deal of unpredictability in the detection of gene expression in blood, for example, in order to diagnose cancer. Gormally et al. (Mutation Res., vol. 635, pp. 105-117, 2007) in a recent review examined the utility of the detection of circulating DNA in blood for cancer diagnosis. They concluded that even though it seems to be a promising way towards non-invasive cancer detection, there are several significant obstacles to its use, namely, the amount of DNA present in circulation (page 107, third paragraph), presence of high levels of circulating DNA in patients with inflammatory diseases (page 108, first paragraph) and the possibility that a large amount of circulating DNA originates from healthy cells (page 109, second paragraph), as well as uncertainty as to the diagnostic or prognostic value of circulating DNA (page 112, last paragraph; page 113, first paragraph). Gormally et al. conclude with the following (page 114, last paragraph):

"As concluding remarks, we would like to formulate recommendations for future studies on CFDNA. First, it is essential to develop quantitative approaches to determine the load of DNA alterations in CFDNA, and to establish the lower detection limit of the methodologies used. This will be crucial to determine cut-off values for the significance of the detection of DNA alterations. Second, future studies should consider the inclusion of different genes and types of alterations to increase both sensitivity and specificity for cancer detection. Third, systematic comparisons should be performed between different cancers to determine whether some cancer types are more prone than others to release altered CFDNA. In particular, systematic studies should be developed to compare CFDNA with other surrogate source of DNA such as sputum for lung cancer or urine for bladder cancer. Fourth, it would be very important to develop large-scale studies based on case–control and/or prospective study designs, rather than on the analysis of consecutively recruited clinical cases. Fifth, the translation of experimental CFDNA studies into epidemiological and

clinical practice will require the development of instrumentation and methods adapted to large-scale, low cost analysis of mutations in very small amounts of DNA."

Considering the fact that SOX4 is overexpressed in other types of cancer, such as salivary adenoid cystic carcinoma, as evidenced by Frierson et al. (Am. J. Pathol., vol. 161, pp. 1315-1323, 2002; page 1318, Fi.2 and Table 1), and in bladder carcinoma and other cancers, as evidenced by Aaboe et al. (Cancer Res., vol. 66, pp. 3434-3442, 2006; page 3434, third and fourth paragraphs; Fig.1; page 3439, last paragraph; page 3440, first paragraph), detection of SOX4 transcripts or DNA in blood would not lead to diagnosis of the site of the disease.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this method to detection of prostate cancer or discrimination between tumor types using any level of expression of SOX4 in any tissue, or using any level of expression of any sequence which hybridizes to SEQ ID NO: 43 at high stringency. For example, in the latter case the levels of expression of about 20 genes would need to be determined in all possible biological samples and correlated with the presence of prostate cancer or a specific type of prostate tumor in a population sample large enough to produce statistically significant results. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where level of expression of a given polynucleotode depends upon numerous known and unknown parameters, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art

and the specification provides insufficient guidance to overcome the art recognized problems in the use of the polynucleotides in blood, for example, for cancer detection. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

9. Claims 1, 2 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Schlegel et al. (WO 2003/009814 A2).

Regarding claims 1 and 5, Schlegel et al. teach detection of overexpression of SOX4 (SEQ ID NO: 380, 99.9% identical to SEQ ID NO: 43; see sequence search) in prostate tumors and utility of the sequence to detect metastatic tumors (page 3, lines 6-20; page 4, lines 8-17; page 9, lines 12-21; Table 1, page 15; Table 3, page 24).

Regarding claim 2, Schlegel et al. teach detection of mRNA (page 36, lines 1-11).

10. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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July 16, 2008